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Review

Influenza virus resistance to neuraminidase inhibitors

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ABSTRACT

In addition to immunization programs, antiviral agents can play a major role for the control of seasonal influenza epidemics and may also provide prophylactic and therapeutic benefits during an eventual pandemic. The purpose of this article is to review the mechanism of action, pharmacokinetics and clinical indications of neuraminidase inhibitors (NAIs) with an emphasis on the emergence of antiviral drug resistance. There are two approved NAIs compounds in US: inhaled zanamivir and oral oseltamivir, which have been commercially available since 1999–2000. In addition, two other NAIs, peramivir (an intravenous cyclopentane derivative) and laninamivir (a long-acting NAI administered by a single nasal inhalation) have been approved in certain countries and are under clinical evaluations in others. As for other antivirals, the development and dissemination of drug resistance is a significant threat to the clinical utility of NAIs. The emergence and worldwide spread of oseltamivir-resistant seasonal A(H1N1) viruses during the 2007–2009 seasons emphasize the need for continuous monitoring of antiviral drug susceptibilities. Further research priorities should include a better understanding of the mechanisms of resistance to existing antivirals, the development of novel compounds which target viral or host proteins and the evaluation of combination therapies for improved treatment of severe influenza infections, particularly in immunocompromised individuals. This article forms part of a symposium in *Antiviral Research* on "Treatment of influenza: targeting the virus or the host."

Contents

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1. Introduction

Two classes of antiviral drugs are currently approved for the management of influenza infections: the adamantanes and the neuraminidase inhibitors (NAIs). The adamantane drugs or matrix (M)-2 blockers, amantadine and rimantadine, were developed in the 1960s and approved since then in many countries. Due to their activity against influenza A viruses only, their adverse effects, and the rapid emergence of resistance either during treatment or in the absence of drug pressure, the Centers for Disease Control and Prevention (CDC) has strongly advised against the use of this class of drugs (CDC, 2006). Hence, since 2010, the neuraminidase inhibitors are the only class of antivirals recommended by the WHO for the treatment and prophylaxis of influenza A and B infections (Pizzorno et al., 2011a).

Two NAIs are currently licensed worldwide for therapeutic and prophylactic uses: the oral agent oseltamivir phosphate, commercially available as Tamiflu (F. Hoffmann-La Roche) and the inhaled drug zanamivir, which is commercially available as Relenza (GlaxoSmithKline). During the 2009 influenza pandemic, the U.S. Food and Drug Administration (FDA) issued an Emergency Use Authorization (EUA) for the parenteral drug peramivir (BioCryst) for the treatment of hospitalized patients with known or suspected influenza A(H1N1)pdm09 infection (Birnkrant and Cox, 2009). Peramivir is approved in Japan as Rapiacta and also available in South Korea as Peramiflu. Laninamivir octanoate (CS-8958), which is a prodrug of laninamivir (another inhaled NAI with long-acting properties), has also been approved in Japan and is commercially available under the name of Inavir (Daiichi Sankyo Company Ltd.). The latter two NAIs are currently in clinical evaluation in US and other countries. In this article, we review the mechanism of action, pharmacokinetics and clinical indications of NAIs with an emphasis on the emergence of antiviral drug resistance.

2. Mechanism of action of NAIs

Along with the hemagglutinin (HA), the neuraminidase (NA) is the other major influenza surface antigen. The latter is a mushroom-shaped homotetrameric glycoprotein with a stalk domain anchored to the viral membrane and a globular head that contains a catalytic site. While the HA protein is responsible for virus attachment to the sialic acid receptors on the host cell, the catalytic activity of the NA cleaves off the terminal *N*-acetyl neuraminic acid (Neu5Ac) on these 2,3 and 2,6 sialic acid moieties. Therefore, the enzymatic activity of the influenza NA plays a key role in releasing progeny virions from the host cell and also in facilitating viral spread throughout the upper airways by cleaving off the sialic acid on the mucin of respiratory mucus.

Given its catalytic function, the structure of the NA active site is highly conserved among influenza A and B viruses, and hence constitutes an attractive target for antiviral therapy. The crystallographic data of NAs from N2 (Colman et al., 1983), N9 (Baker et al., 1987) and B (Burmeister et al., 1992) viral backgrounds

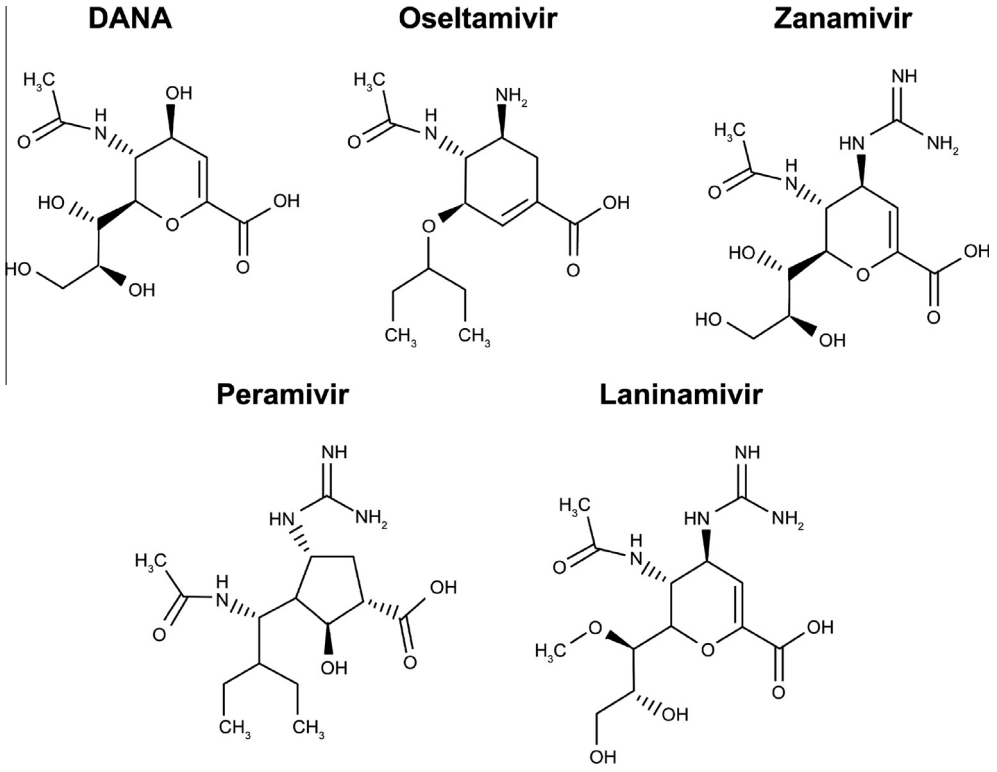

Fig. 1. Chemical structure of neuraminidase inhibitors (NAIs). All these agents are based on the structure of the 2,3-didehydro analog of the *N*-acetyl-neuraminic acid (DANA). The bioavailable prodrug of oseltamivir is an ethyl ester that is converted into the active carboxylate by hepatic esterases. Zanamivir is a 4-deoxy-4-guanidino analog of DANA. Peramivir is a cyclopentane derivative with a guanidinyl group and a lipophilic chain. Laninamivir is the active product of the esterified octanoate CS-8958. These molecules interact differently within the enzyme active site, which may influence their antiviral activity.